## REMARKS

Claims 10, 20 and 26-29 are pending and under consideration. Claims 26 and 27 are currently amended. Claims 1-9, 11-19, 22, and 24 have been canceled. Claims 21, 23 and 25 are withdrawn. Support for the claim amendment may be found throughout the specification and claims as originally filed, including, for example, at least in the specification as originally filed on page 9, lines 20-31. No new matter is added.

Amendment of the originally filed claims, or cancellation of any claims should in no way be construed as an acquiescence, narrowing, or surrender of any subject matter. The amendments are being made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicants reserve the right to pursue the subject matter of the canceled claims in this application or a subsequently filed application.

### 35 U.S.C. § 103

The Office rejected claims 10, 20 and 26-29 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Agrawal et al. (U.S. Patent No. 5,856,462), Kreig et al. (Biochimica et Biophysica Acta 1489:107-116 (1999)), and Monia et al. (U.S. Patent No. 6,159,697). In particular, the Office states that "Monia et al. teach antisense compounds targeted to the Smad7 gene and further teach methods of identify efficient target sites and generating antisense oligonucleotides capable of inhibiting the expression of Smad7." The Office concludes that one of skill in the art would have been capable of generating the claimed antisense compound based on the Smad7 cDNA sequence and methods disclosed by Monia, and the modifications of oligonucleotides taught by Agrawal and Krieg. Applicants respectfully traverse the rejection.

In contrast to the Office's assertion, Monia does not teach a method for identifying efficient target sites in Smad7 for modulation by antisense oligonucleotides. Rather, Monia states:

> The [targeting] process usually begins with the identification of a nucleic acid sequence whose function is to be modulated. ... The targeting process also includes determination of a site or sites within this gene for the antisense interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result.

> Within the context of the present invention, a preferred intragenic site is the region encompassing the translation initiation or termination codon of the open reading frame (ORF) of the gene. ... The open reading frame (ORF) or "coding region" … is also a region which may be targeted effectively. Other target regions include the 5' untranslated region (5' UTR) … and the 3' untranslated region (3' UTR)…. The 5' cap region may also be a preferred target region. … mRNA splice sites … may also be preferred target regions…. Aberrant fusion junctions due to rearrangements or deletions are also preferred targets. It has also been found that introns can also be effective, and therefore preferred, target regions for antisense compounds targeted, for example, to DNA or pre-mRNA. Once one or more target sites have been identified, oligonucleotides are chosen which are sufficiently complementary to the target, i.e., hybridize sufficiently well and with sufficient specificity, to give the desired effect. (See Monia, U.S. Patent No. 6,159,697, columns 3 and 4.)

Although the target sequence disclosed by Monia is Smad7, based on this disclosed targeting process, an antisense oligonucleotide to Smad7 could be targeted anywhere in an open reading frame, the 5' untranslated region, the 3' untranslated region, the 5' cap region, mRNA splice sites, or an intron. Thus, except for the specific antisense oligonucleotides disclosed in Tables 1 and 2, the skilled person reading Monia would have no guidance where to target and select a specific antisense oligonucleotide in Smad7. Based on the purported target selection method by Monia, the potential options for identifying and selecting a target sequence against Smad7 would be infinite (*e.g.*, the oligonucleotide could vary in target site selection, length, nucleotide composition, modifications and/or potential substitutions). In addition, the skilled person reading Monia would not be able to predict which of these potential antisense oligonucleotide sequences would be capable of modulating (*e.g.*, inhibiting) Smad7 expression. Further, the skilled person reading Monia would not be able to predict which of these sequences would be most useful as a pharmaceutical composition for modulating (*e.g.*, inhibiting) Smad7 expression in a subject. Moreover, as acknowledged by the Office, Monia does not teach SEQ ID NO:15 as claimed in the instant application. Still further, the Office has also acknowledged that Monia does not teach or suggest the incorporation of CpG motifs as claimed in the instant application.

Agrawal and Kreig do not cure the deficiencies of Monia. The Office relies on Agrawal for the teaching of modified CpG oligonucleotides, methylene phosphonate linkages, oligonucleotides containing RNA or 2'-O-substituted RNA, and the use of pharmaceutically acceptable carriers in a pharmaceutical composition. In addition, the Office relies on Kreig for the teaching that "immune stimulation may be avoided in antisense oligonucleotides by the use of modified backbones and selective modification of the cytosine nucleotides in any CpG

dinucleotide" (see Office Action, page 4). However, neither Agrawal nor Kreig teach or suggest an antisense oligonucleotide against Smad7 comprising SEQ ID NO:15 as claimed in claim 1.

Therefore, the combination of references, *e.g.*, Monia, Agrawal, and Kreig, fails to teach or suggest the claimed subject matter taken as a whole. Thus, Applicants respectfully request that the rejection be withdrawn.

## CONCLUSION

Applicants respectfully request reconsideration of the rejections and allowance of pending claims. The Examiner is invited to call the undersigned at the telephone number below if this communication does not place the case in condition for allowance, or if there are any questions regarding this case.

Respectfully submitted,

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